

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 99-178 are pending in the application, with claims 99, 123, 131, and 154 being the independent claims. Claims 1-98 are sought to be cancelled by the present amendment without prejudice to or disclaimer of the subject matter therein. New claims 99-178 are sought to be added.

Support for new claims 99-178 may be found in original claims 55-98 and on various pages of the as-filed application. For example, support for isomerizing a mixture of *trans/cis* isomers of the compound of Formula I (or Formula IV) to give the ratio of *trans/cis* of about 85/15 or greater, e.g. by treating with L⁻ or heating the mixture of *trans/cis* isomers, or by isolating the *cis* isomer from the mixture and treating the *cis* isomer with L⁻, to form an enantiomerically enriched compound of Formula I (or Formula IV) wherein the ratio of *trans/cis* is about 85/15 or greater, may be found in the specification, for example, at page 24, lines 1-23, and in claim 25 as originally filed.

Support for "M is attached to phosphorus via an oxygen present in a hydroxyl group on an acyclic sugar in MH" may be found in the specification, for example, at page 30, lines 11-12.

Support for new claims 160 and 161 can be found in the specification, for example, at page 12, lines 5-6 and 14-15.

Support for new claims 102, 126 and 134 may be found in the specification, for example, at page 23, line 26, to page 24, line 23.

Support for new claims 122, 154, and 178 may be found at page 26, line 21, to page 30, line 13.

These changes are believed to introduce no new matter and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 57, 61, 67, 74, 78, 84, 92, 94 and 97 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (Office Action, at page 2, lines 17-19.) Applicants respectfully traverse this rejection.

Claims 57, 61, 67, 74, 78, 84, 92, 94 and 97 have been canceled. New claims 99-178 do not contain the allegedly indefinite language.

Applicants assert that the rejection of claims 57, 61, 67, 74, 78, 84, 92, 94 and 97 under 35 U.S.C. § 112, second paragraph, has been overcome or rendered moot and respectfully request that the Examiner reconsider and withdraw this rejection.

II. Rejections under 35 U.S.C. § 102

Claims 55-60, 66-67, 74-79, 82-87, and 97-98 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Erion *et al.*, WO 99/45016. (Office Action, at page 4, lines 1-2.) Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that on pages 73-77, Erion *et al.* discloses Applicants' claimed process of making prodrugs by reacting the phosphorylating agent of

Formula I with MH in the presence of a base. (Office Action, at page 4, lines 3-4.) The Examiner states that "MH is nucleoside or any bioactive agent or drug. M is attached to P via O, C, N or S. See the entire document particularly, pages 54-55, 62-63, the examples and claims." (Office Action, at page 4, lines 4-6.)

Claims 55-60, 66-67, 74-79, 82-87, and 97-98 have been canceled thus rendering moot this rejection. In the interest of expediting the prosecution of the present application, Applicants offer the following comments regarding the rejection as it may apply to new claims 99-178.

Applicants claimed invention is directed to methods for producing *cis*-cyclic phosphate prodrugs using enantiomerically enriched *trans*-phosphorylating reagents of Formula I. The *trans*-phosphorylating reagents are synthesized using 1-aryl-3-propane diols and enantiomerically enriched during synthesis by isomerization.

For example, new claim 99 requires obtaining an enantiomerically enriched *trans*-phosphorylating reagent of Formula I, wherein the ratio of *trans/cis* is about 85/15 or greater, by isomerizing a mixture of *trans/cis* isomers of the compound of Formula I to give the ratio of *trans/cis* of about 85/15 or greater, and then reacting the enantiomerically enriched compound of Formula I with MH to produce the *cis*-cyclic prodrugs of Formulae II.A and II.B.

Erion *et al.* does not teach, or even suggest, producing an enantiomerically enriched *trans*-phosphorylating reagent of Formula I, wherein the ratio of *trans/cis* is about 85/15 or greater, by isomerizing a mixture of *trans/cis* isomers of the phosphorylating reagent. For example, at page 74, line 21, to page 76, line 2, Erion *et al.* describes the synthesis of chiral activated phosphorylating reagents. At page 74, lines

22-27, Erion *et al.* states that the reaction to produce the phosphorylating reagent produces two diastereomeric intermediates (the *cis* and *trans* isomers) "that can be separated by a combination of column chromatography and/or crystallization." In the claimed method, however, the *trans*-enriched phosphorylating reagent is produced during synthesis, e.g., by isomerizing the *cis* isomers of the phosphorylating reagent to the *trans* form in the *cis/trans* mixture. Since Erion *et al.* does not teach this element of the claims, Erion *et al.* cannot anticipate the claimed invention.

Applicants believe that the rejection of claims 55-60, 66-67, 74-79, 82-87, and 97-98 under 35 U.S.C. §102 has been overcome or rendered moot and respectfully request that the Examiner reconsider and withdraw the rejection.

III. Rejections under 35 U.S.C. § 103

Claims 55-60, 66-67, 74-79, 82-87, and 97-98 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Erion *et al.*, WO 99/45016. (Office Action, at page 4, lines 15-16.) Applicants respectfully traverse this rejection.

Specifically, the Examiner states that Applicants' claimed method is *prima facie* obvious from the teaching of Erion *et al.* because "[d]ifferent substituents of the phosphorylating agent which are optionally protected make the instant phosphorylating agent analogous to the phosphorylating agent of Erion *et al.*, and using an analogous starting material in a well-known process is *prima facie* obvious." (Office Action, at page 5, lines 5-9.) The Examiner concludes that "[o]ne of ordinary skill in the art would have known to use analogous reagent at the time the invention was made. The

motivation for using analogous nucleoside is from the teaching of Erion *et al.*, that MH is any nucleoside, bioactive agent or drug." (Office Action, at page 5, lines 9-11.)

Claims 55-60, 66-67, 74-79, 82-87, and 97-98 have been canceled thus rendering moot this rejection. In the interest of expediting the prosecution of the present application, Applicants offer the following comments regarding the rejection as it may apply to new claims 99-178.

For the reasons discussed above, Erion *et al.* does not teach or suggest producing an enantiomerically enriched *trans*-phosphorylating reagent of Formula I, wherein the ratio of *trans/cis* is about 85/15 or greater, by isomerizing a mixture of *trans/cis* isomers of the phosphorylating reagent of Formula I to give the ratio of *trans/cis* of about 85/15 or greater. Thus, Applicants assert that the Examiner has failed to establish that Applicants' claimed methods are *prima facie* obvious over Erion *et al.*

Applicants believe that the rejection of claims 55-60, 66-67, 74-79, 82-87, and 97-98 under 35 U.S.C. § 103 has been overcome or rendered moot and respectfully request that the Examiner reconsider and withdraw the rejection.

IV. Double Patenting Rejection

Claims 55-98 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 83-91 of U.S. Patent No. 6,312,662, Erion *et al.* ("the '662 patent"). (Office Action, at page 5, line 27, to page 6, line 2.) Applicants respectfully traverse this rejection.

Claims 55-98 have been canceled thus rendering moot this rejection. In the interest of expediting the prosecution of the present application, Applicants offer the following comments regarding the rejection as it may apply to new claims 99-178.

As discussed above, Applicants' claimed invention is directed to methods for producing *cis*-cyclic phosphate prodrugs using enantiomerically enriched *trans*-phosphorylating reagents of Formula I, which are produced by isomerizing a mixture of *trans/cis* isomers of the phosphorylating reagent to produce the enantiomerically enriched *trans*-phosphorylating reagent having a *trans/cis* ratio of about 85/15 or greater. The '662 patent does not teach, or even suggest, producing an enantiomerically enriched *trans*-phosphorylating reagent of Formula I by isomerizing a mixture of *trans/cis* isomers of the phosphorylating reagent as required in pending claims 99-178.

Thus, Applicants respectfully disagree with the Examiner and assert that the '662 patent provides no suggestion to make *cis*-cyclic phosphate prodrugs using Applicants' claimed method, and that the methods of making the prodrugs claimed in the '662 patent, and Applicants' claims 99-178, are patentably distinct from one another.

Applicants believe that the rejection of claims 55-98 under the judicially created doctrine of obviousness-type double patenting has been overcome and respectfully request that the Examiner reconsider and withdraw the rejection.

V. Objection to the Specification

The Examiner objects to the specification for allegedly having "numerous abbreviations, which are not common chemical nomenclature and are not defined in the

specification on first occurrence in accordance with the standard scientific practice."

(Office Action, at page 6, lines 4-6.)

Applicants respectfully direct the Examiner's attention to pages 14-17 of the specification, where definitions are provided for many of the chemical abbreviations used in the specification. Moreover, new claims 115, 120, 151 and 175 provide full chemical names for the terms LDS, LHMDs, t-BuOK, DBU, DABCO, MOM and MEM. Applicants believe that any additional abbreviations occurring in the specification that are not explicitly defined are known to those of skill in the art and, accordingly, would not require inclusion of a definition. However, if the Examiner believes that there are any additional abbreviations that require definitions, Applicants invite the Examiner to identify these abbreviations so that Applicants may better address the Examiner's objection to the specification.

Applicants believe that the objection to the specification has been overcome and respectfully request that the Examiner reconsider and withdraw the objection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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